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Neuromonitoring in Critically Ill Patients

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OBJECTIVES: Critically ill patients are at high risk of acute brain injury. Bedside multimodality neuromonitoring techniques can provide a direct assessment of physiologic interactions between systemic derangements and intracranial processes and offer the potential for early detection of neurologic deterioration before clinically manifest signs occur. Neuromonitoring provides measurable parameters of new or evolving brain injury that can be used as a target for investigating various therapeutic interventions, monitoring treatment responses, and testing clinical paradigms that could reduce secondary brain injury and improve clinical outcomes. Further investigations may also reveal neuromonitoring markers that can assist in neuroprognostication. We provide an up-to-date summary of clinical applications, risks, benefits, and challenges of various invasive and noninvasive neuromonitoring modalities.

DATA SOURCES: English articles were retrieved using pertinent search terms related to invasive and noninvasive neuromonitoring techniques in PubMed and CINAHL.

STUDY SELECTION: Original research, review articles, commentaries, and guidelines.

DATA EXTRACTION: Syntheses of data retrieved from relevant publications are summarized into a narrative review.

DATA SYNTHESIS: A cascade of cerebral and systemic pathophysiological processes can compound neuronal damage in critically ill patients. Numerous neuromonitoring modalities and their clinical applications have been investigated in critically ill patients that monitor a range of neurologic physiologic processes, including clinical neurologic assessments, electrophysiology tests, cerebral blood flow, substrate delivery, substrate utilization, and cellular metabolism. Most studies in neuromonitoring have focused on traumatic brain injury, with a paucity of data on other clinical types of acute brain injury. We provide a concise summary of the most commonly used invasive and noninvasive neuromonitoring techniques, their associated risks, their bedside clinical application, and the implications of common findings to guide evaluation and management of critically ill patients.

CONCLUSIONS: Neuromonitoring techniques provide an essential tool to facilitate early detection and treatment of acute brain injury in critical care. Awareness of the nuances of their use and clinical applications can empower the intensive care team with tools to potentially reduce the burden of neurologic morbidity in critically ill patients.

KEY WORDS: electroencephalography; intracranial pressure; multimodality monitoring; neuromonitoring; transcranial Doppler

Critically ill patients are predisposed to an ongoing risk of secondary brain injury (SBI) from primary brain pathology as well as from systemic derangements like acidosis, hypoxia, and ischemia (1). The CNS has been a consistent focus of physiologic monitoring, partly due to the significant impact of neurologic morbidities on quality of life after recovery from

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KEY POINTS

Question: What are the most commonly used neuromonitoring modalities in critical care? What are the risks in using these modalities? What are their evidence-based clinical applications in critical care?

Findings: A myriad of invasive and noninvasive neuromonitoring modalities are available for use in critical care that can provide targets for therapeutic interventions to prevent and treat secondary brain injury. These modalities are also being researched to provide markers for neuroprognostication.

Meanings: Multimodality neuromonitoring can potentially facilitate early detection and treatment of acute brain injury in critical care.

critical illness. Early detection and treatment of acute brain injury (ABI) and prevention of SBI is paramount in critically ill patients. Neuromonitoring techniques with bedside data visualization allow continuous assessments of cerebral physiology, and early identification of treatment targets, before neuronal damage becomes irreversible (2).

We provide a narrative review of the current state of knowledge in neuromonitoring techniques, highlighting their clinical indications and implications of use in critically ill patients. Using the analogy of a house, we have described various neuromonitoring modalities into four main classes: "structural framework"—neurologic assessments, automated pupillometry (AP), and neuroimaging that assess structural integrity of brain parenchyma; "plumbing and pressure framework"—cerebral blood flow (CBF), intracranial pressure (ICP), cerebral perfusion pressure (CPP), cerebral oximetry, and autoregulation assessment; "electrical framework"—electroencephalography (EEG) and evoked potentials that assess electrophysiology of central and peripheral nervous system; and "air or composition"—brain biochemistry including cerebral microdialysis (CMD) and biomarkers that may represent the other miscellaneous components in the house (**Fig. 1**). Multimodality monitoring (MMM) is the simultaneous monitoring of multiple physiologic variables to get a full picture of the pathophysiology of the brain and a full assessment of the "house" as a whole.

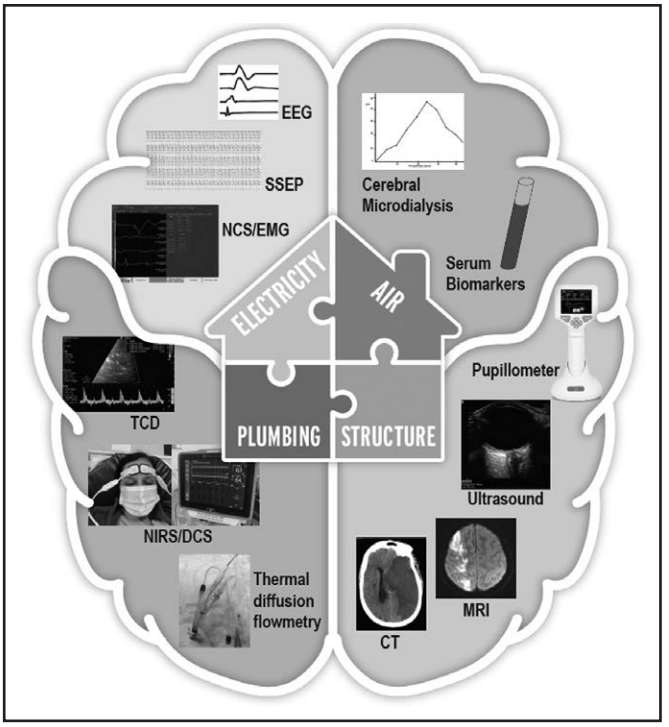

Figure 1. Pictorial representation of major physiologic compartments of the cranium analogous to components of a house that inform neuromonitoring. The electrical grid is represented by electroencephalography (EEG), somatosensory evoked potentials (SSEPs), nerve conduction studies (NCS), and electromyography (EMG). Plumbing pressures/perfusion is represented by cerebral blood flow assessed by transcranial Doppler (TCD), near-infrared spectroscopy (NIRS), thermal diffusion flowmetry, and jugular venous oxygen saturation (not shown). Structure is represented by automated pupillometry, optic nerve sheath ultrasound, and other neuroimaging modalities. Air/composition is signaled by serum biomarkers and cerebral microdialysis. DCS = diffuse correlation spectroscopy.

STRUCTURAL ASSESSMENT

Neurologic Examination

The bedside neurologic examination is the first and the most essential component in neuromonitoring. The intent of clinical neurologic examination is to detect neurologic changes early enough to institute interventions to reduce significant SBI. It also aids in localization of injury, whether it is focal or global, involving the central or peripheral nervous system, which guides diagnostic testing and treatment. Critically ill patients with impairment of consciousness are difficult to monitor with a clinical neurologic examination alone given its low sensitivity and inter-rater reliability in such patients, although posturing motor response is a commonly recognized sign of cerebral herniation (3).

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Clinical scoring scales like the Glasgow Coma Scale and Full Outline of Unresponsiveness Score have been developed to monitor the overall neurologic status of critically ill patients but are limited by the inability to detect localizing deficits. The National Institute of Health Stroke Scale focuses on localization of language, motor, and sensory deficits and can be applied to patients suspected of having an acute cerebrovascular event within the acute window of an acute intervention. Current consensus recommends that a complete neurologic examination should be conducted at least daily with daily interruption in sedation, when applicable, in all critically ill patients, irrespective of their presenting diagnosis (4–7). A more detailed neurologic examination can follow in patients with deficits. The frequency and complexity of the examination can be tailored to the risk of neurologic deterioration, keeping in mind that prolonged frequent neurologic assessments over days can predispose the patient to lack of sleep and increase the risk of delirium (1). **Supplementary Figure 1** (http://links.lww.com/CCM/H285) shows a practical example of frequent assessments in a neurocritical care unit for patients at risk of neurologic deterioration. Certain elements of the neurologic examination may be helpful in neurologic prognostication, when used in a multimodality approach (8). A neurologic examination limited by a decreased level of consciousness or analgosedation can be an indication for additional neuromonitoring techniques. (3). Technological advances in neuromonitoring provide adjunctive or additional, or perhaps earlier, methods to detect neurologic changes or decline.

Automated Pupillometry

Pupillary size and pupillary light reflex (PLR) impairment have a physiologic association with intracranial hypertension in ABI (8, 9). Traditionally used flashlight-based measurements have significant interoperator variability, necessitating investigation into automated pupil assessments (3, 10–13). AP is a portable, user-friendly, handheld infrared optical scanner that quantitatively measures pupillary size, constriction velocity, and neurologic pupil index (NPi), a proprietary metric derived from PLR (**Fig. 2**). AP adds objectivity and consistency to the pupillary examination. In addition, subtle pupillary changes better detected by AP may precede clinical deterioration. Pupillary metrics using AP may assist in neuroprognostication. Normal PLR measured using AP has been associated with improved neurologic outcomes after cardiac arrest, hemicraniectomy, and successful treatment for nonconvulsive status epilepticus (8, 9, 14–18). There is a need for high-quality evidence, especially one correlating its use with clinical outcomes, before wider acceptance of this device. Other limitations include a higher price compared with a flashlight and measurements that vary depending on the amount on ambient light in the room, orbital pathology, agitation, or medications (9, 15).

Neuroimaging

Emergent neuroimaging such as CT or MRI can provide vital information regarding the "structural integrity" of the brain to assess for new or worsening structural brain damage, assess for potentially salvageable tissue, and determine the severity of brain injury to assist in neuroprognostication (**Fig. 3**; and **Supplementary Fig. 2**, http://links.lww.com/CCM/H285) (19). Radiological imaging is also integral to deciding the appropriate location and checking the placement of invasive neuromonitoring devices. Despite technological advances allowing portable bedside CT and MRI, round-the-clock availability of these resources remains scarce in most institutions (20). Intensive care professionals are encouraged to seek further resources for learning neuroimaging as a valuable complement to bedside neuromonitoring techniques.

PLUMBING, PRESSURE, OXYGEN, AND AUTOREGULATION

Cerebral Blood Flow

Transcranial Doppler Ultrasonography. Transcranial Doppler (TCD) allows noninvasive static or dynamic assessment of CBF using a low-frequency (1–3 MHz) ultrasound transducer placed on the scalp (**Fig. 4**; **Supplementary Fig. 3**, http://links.lww.com/CCM/H285). TCD is used in critical care to detect abrupt changes in vasculature caused by stenosis or spasm affecting cerebral hemodynamics; to detect active embolic signals; to continuously monitor CBF in response to systemic hemodynamic changes to detect cerebral autoregulation (CA); and to assess cerebral perfusion as a noninvasive surrogate of ICP. TCD-derived CBF

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Figure 2. Bedside neuromonitoring techniques showcase the "structure" and "plumbing" of a "house." **A**, An automated pupilometer (AP) measures fluctuations in pupillary light reflex (PLR) in response to a stimulus (NPi-300 NeurOptics, Irvine, CA). **B**, The quantitative output from AP shown here includes neurologic pupil index (NPi), a proprietary mathematical algorithm based on quantitative PLR measurements and individual pupil sizes at rest, with difference between pupils highlighted for each measurement. (Images courtesy of Alexandra Reynolds, MD). **C**, Near-infrared spectroscopy (NIRS) noninvasive bedside measurement of direct regional cerebral arteriovenous (mixed) brain oxygenation (Foresight tissue oximetry system; Edwards Lifesciences Corporation, Irvine, CA). **D**, NIRS values shown for each side of the cranium that can be visualized along with systemic parameters like cardiac output and cardiac index. (Image courtesy of Bryan Marchant, MD, permission from standardized patient granted). ID = identification.

velocity can be a useful complement to the clinical examination and has been used as a screening tool and surrogate marker for vasospasm in patients with aneurysmal subarachnoid hemorrhage (aSAH) at risk of delayed cerebral ischemia before clinical deterioration (Supplementary Fig. 3, http://links.lww.com/CCM/H285) (1, 6, 21–23). In the evaluation of clinically significant vasospasm, Middle Cerebral Artery velocities greater than 200 cm/s, a daily increase in velocity by 50 cm/s or Lindegaard ratio (middle cerebral artery velocity/extracranial internal cerebral artery velocity) greater than 6 have a high positive predictive value, and normal velocities less than 80 cm/s have a high negative predictive value (21, 24, 25). American Heart/

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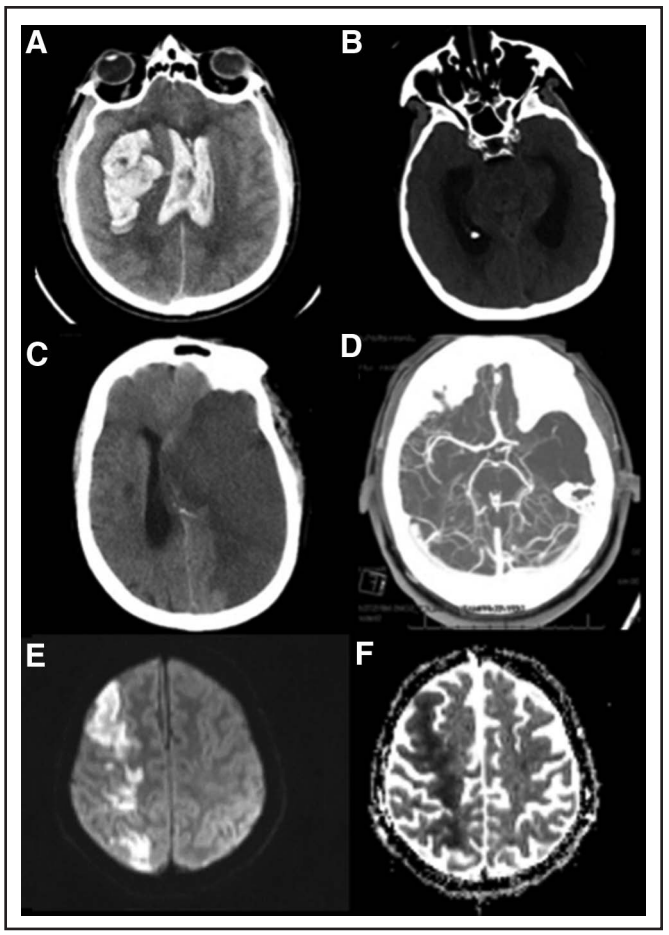

Figure 3. A, CT brain axial section images of intracranial and intraventricular hemorrhage with a hyperdense appearance. **B**, Hydrocephalus visualized as dilation of the lateral ventricles that compresses the brain stem in the center. **C**, Acute ischemic stroke or acute cytotoxic edema from infarction may be undetectable early on but over hours distinguishes itself with a hypodense appearance, typically in the distribution of an arterial distribution, in this case, left middle cerebral territory (MCA) infarction. Ipsilateral ventricle is effaced with relative dilation of right lateral ventricles. **D**, Corresponding CT angiography images showing large vessel occlusion of left MCA, causing this infarction. **E**, MRI of brain showing a diffusion weight imaging (DWI) sequence with (**F**) showing corresponding apparent diffusion coefficient (ADC) images can detect cytotoxic edema within minutes. Infarction appears white on DWI with a corresponding black area on ADC. In this image, the distribution of infarction corresponds to watershed territory between the MCA and the anterior cerebral artery.

Stroke Association guidelines recommend using TCD to monitor for arterial cerebral vasospasm in the management of aSAH (class IIa, level B), though traumatic subarachnoid can also be monitored with TCD to detect delayed cerebral ischemia (26). The limited availability of TCD expertise and the low specificity of TCD in detecting spasm with moderate elevations in velocity have dissuaded universal application in SAH management. TCD is the only dynamic modality that can help visualize microemboli signals going to the brain from intracranial or central sources and stratify the risk for recurrent strokes in patients with embolic phenomena (Fig. 4) (27, 28). TCDs' ability to diagnose intra- or extra-cardiac shunts can also elaborate on the pathophysiology of neurologic deterioration in systemic illness (29).

Use of TCD in assessing cerebral vasoreactivity and as a noninvasive surrogate for ICP is detailed below in the section, "Cerebral autoregulation" and "Intracranial pressure" and "cerebral perfusion pressure," respectively. Emerging incorporation of point-of-care ultrasound in critical care now incorporating TCD may increase availability and expertise in its bedside application. Automated robotic TCD machines have the potential to allow continuous monitoring, allowing widespread use (30–32).

Other attempts to assess CBF noninvasively using ultrasound-tagged near-infrared spectroscopy (c-FLOW; Ornim Medical, Lod, Israel) have revealed too much variability in thresholds and thus have not been widely adopted (33). Traditional perfusion imaging modalities like CT perfusion (Supplementary Fig. 2, http://links.lww.com/CCM/H285), Xenon-enhanced CT, or Positron Emission Tomography are noninvasive but not ideal bedside neuromonitoring devices, as they are limited by their inability to perform serial assessments and the need for IV contrast (34).

Thermal Diffusion Flowmetry. Thermal diffusion flowmetry (TDF)-based invasive intraparenchymal (IP) monitors are typically inserted in tissue at-risk to yield direct regional measurement of CBF with high temporal resolution (**Fig. 5**). This can aid in the real-time diagnosis of ischemia or hyperemia that can guide ICP/CPP-targeted therapies to potentially reduce SBI. When used in conjunction with ICP/CPP/brain tissue oxygen tension ($Pbto_2$) monitoring and CMD, TDF-based CBF can be a useful target to ensure substrate delivery is coupled to the metabolic demands of the individual brain. A commonly accepted threshold is maintaining a CBF of greater than 20 cm^3/100 g/min, but CBF thresholds should be considered in relevance to autoregulation, as augmentation of CBF in a dysregulated state can cause reperfusion injury. The accuracy of CBF is affected by the location of the probe in proximity to large vessels and brain pyrexia. In addition,

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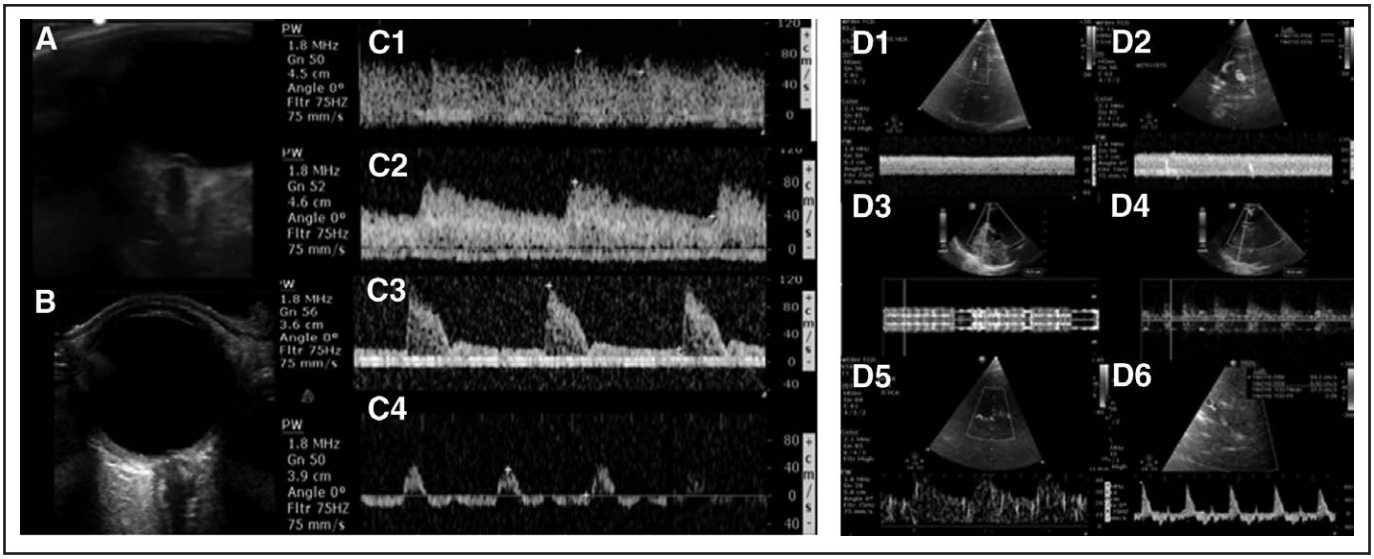

Figure 4. A, Orbital ultrasound with evidence of papilledema manifested as distension of the retina at the site of optic nerve (ON). **B**, Diameter of the ON sheath diameter (ONSD) measured 3 mm behind the retina. A dilated ONSD insonated via orbital ultrasound in a high-risk profile patient may indicate acute intracranial hypertension. **C**, Insonated transcranial Doppler (TCD) waveforms insonated using Pulse Doppler (PW) from the middle cerebral artery (MCA). **C1**, Low-resistance waveforms with very high end-diastolic velocities (EDVs) compared with the systolic flow velocities may represent hyperemia caused by hypercarbia or reperfusion in a dysregulated brain. **C2**, Normal waveform with EDV equal to 1/3rd to 1/2 of peak systolic velocity (PSV) in each cardiac cycle. **C3**, High-resistance waveforms in a patient with high intracranial pressure (ICP) cause a significant drop in the EDV, resulting in very low or absent diastolic flow in relation to the patient's PSV; this is sometimes referred to as a "pre-cerebral-circulatory arrest" pattern. **C4**, Oscillating waveforms with anterograde flow during systole but diastolic flow reversal with retrograde flow from the brain during diastole, with a net zero flow where patient's ICP is much higher than their systemic diastolic pressure. **D1** and **D2**, TCD in a patient on venoarterial extracorporeal membrane oxygenation demonstrate nonpulsatile but normal MCA mean flow velocities (50–60 cm/s) bilaterally. **D3** and **D4**, TCD as a noninvasive surrogate to demonstrate normal perfusion in a patient suspected to have intracranial hypertension, where the external ventricular drain-derived ICP measurements were impaired by high-frequency oscillatory mechanical ventilation. **D5**, Microembolic signals during MCA insonation show active thromboembolic phenomena. **D6**, Oscillating waveforms in a patient with cardiogenic shock who underwent intra-aortic balloon pump placement are incompatible with survival, if sustained.

measurements are susceptible to measurement drift a few days after placement (35). Both extremes of low or high CBF have been associated with poor functional outcomes in observational studies in TBI patients, but no study to date has shown a change in outcomes with TCD-based CBF-targeted interventions (36).

Intracranial Pressure and Cerebral Perfusion Pressure

ICP is typically used as a target for therapy to maintain adequate cerebral perfusion (CPP), calculated as the difference between mean arterial pressure (MAP) and ICP. ICP monitoring is particularly helpful in patients with impaired consciousness or exams confounded by sedation who are at risk for intracranial hypertension and herniation. Qualitative assessment of ICP waveforms, manifest as an increase in the P2 component of the arterial wave or the presence of slow waves termed "Lundberg A" waves, can be a sign of poor intracranial compliance and impending clinical neurologic deterioration from herniation (Fig. 5). Quantitative serial monitoring has used ICP thresholds above 20–25 mm Hg as abnormal, with a large heterogeneity in normative values and thresholds investigated across different clinical types of ABI (37, 38). Intracranial hypertension has been linked to adverse neurologic outcomes and increased mortality after ABI (39–41). But ICP-targeted management has not shown consistent superiority over other clinical paradigms (5, 37, 42). This could be reflective of ICP being a delayed marker of parenchymal injury and a lack of evidence of patient-specific ICP targets for intervention. In addition, CPP calculated using direct ICP measurements may not distinguish hyperemic cerebral perfusion causing high ICPs, and hence may not be amenable to same interventions as perfusion limiting intracranial hypertension (38). A multimodality approach including assessment of cerebral compliance (Fig. 5; **Supplementary Fig. 4**,

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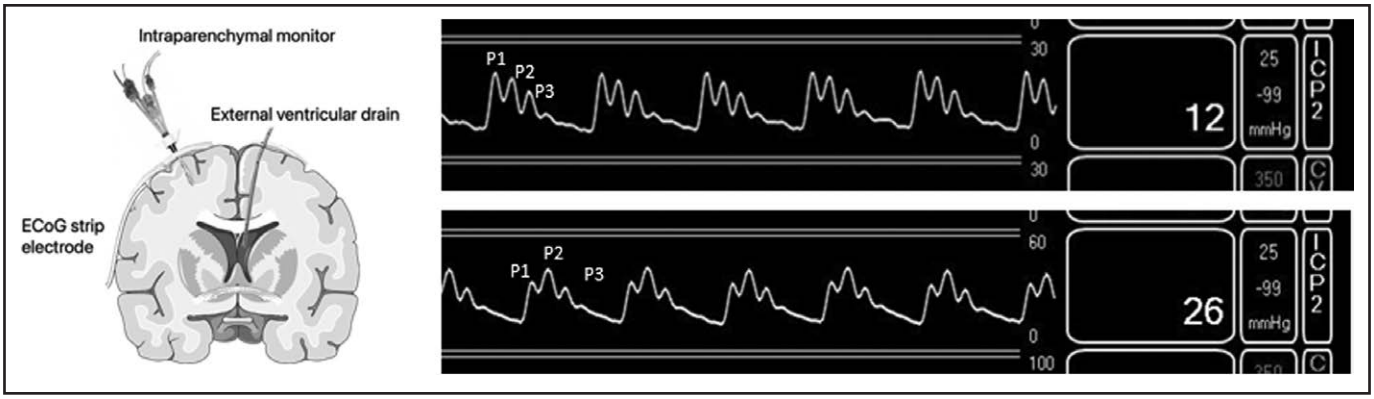

Figure 5. *Left*, Typical location for placing intraparenchymal monitors in the right frontal area in this bundled insertion of intracranial pressure (ICP) monitor, brain tissue oxygen probe, and cerebral blood flow probe through a Richmond bolt in the skull and an external ventricular drainage catheter in the left lateral ventricle. An external ventricular drain to measure intracranial pressure and electrocorticography (ECoG) using an electrode placed directly on the cerebral cortex to record its electrical activity. *Right, upper*: physiologically normal ICP waveforms with downtrending P1, P2, and P3 waves representing arterial pulsation, compliance (tidal) wave and aortic valve closure waves, respectively. ICP measurement is 12 mm Hg. *Right, lower*: Noncompliant waveforms with a second phasic component (P2) higher than the first phase (P1) in systole with an ICP measurement 26 mm Hg. (Brain figure downloaded from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License with image modification to add monitoring devices).

http://links.lww.com/CCM/H285), direct measurement of CBF and cerebral autoregulatory reserve to provide patient-centric ICP goals warrants further assessment (38). Despite these limitations, ICP monitoring is the most commonly used neuromonitoring modality in critically ill patients with impaired consciousness.

Invasive Ventricular and Intraparenchymal ICP Monitors. Continuous invasive ICP monitoring is often done via fluid-coupled external ventriculostomy drains (EVDs), and strain-gauge or fiberoptic-based invasive IP monitors (Fig. 5). An IP monitor may detect early regional ICP changes due to compartmentalization of pressures from the falx and tentorium, compared with a more global ICP measurement by an EVD. However, both devices have shown good correlation on serial monitoring. EVD may be preferentially chosen over IP catheters in patients at risk of hydrocephalus to facilitate cerebrospinal fluid (CSF) drainage, patients presenting with intraventricular hemorrhage (IVH), or patients with indications for intrathecal drug administration such as nicardipine, alteplase, or antibiotics. When used for continuous CSF drainage in hydrocephalus or IVH, EVD can only provide period ICP checks as it needs to be clamped to transduce ICP measurements. When clamped and closed to drainage, it can transduce continuously, as in the setting of TBI. The rates of symptomatic hemorrhage, blockage by drainage tubing by debris or collapsed ventricles, and infection are much higher with EVDs compared with IP monitors due to their larger size and risk of contamination during CSF sampling (43). But EVD can be calibrated when needed, typically at the level of tragus. IP monitors on the other hand, are only calibrated at insertion and may be preferred in patients with global brain injury such as TBI or diffuse cerebral edema with collapsed ventricles who did not or could not receive EVD due to inherent indications. IP monitors are also subject to a drift that makes ICP measurements unreliable after 5–7 days after insertion (44). Like most invasive devices, standardized protocols for placement and care improve the safe use of these devices. Both the EVD and IP monitors can be coupled with brain tissue oxygenation probes placed at the same craniotomy site (refer to section, "Cerebral Oxygenation").

Ultrasonography. ICP monitoring has been attempted noninvasively using ultrasound for detection of papilledema and optic nerve sheath diameter (ONSD) measurement (45). Papilledema assessment performed using ultrasound or fundoscopy, in general, has low sensitivity for acute changes in ICP (Fig. 4) (46, 47). Ultrasound-derived ONSD cutoffs have been shown to be sensitive in detecting acute intracranial hypertension in high-risk patients, but accuracy is limited due to significant heterogeneity in technique, ultrasound resolution, and optic nerve anatomy (Fig. 4) (3, 41, 46, 48). In addition, shift assessment using B-mode ultrasound has also been used as a noninvasive surrogate for ICP (49).

Since ICP measurements are a surrogate for CPP and TCD can directly measure CBF velocities reflecting CPP,

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attempts have been made to derive noninvasive ICPs using TCDs for use in places without access to invasive neuromonitoring. TCDs can be particularly helpful in patients not amenable to invasive ICP monitoring, for example, hepatic encephalopathy, ECMO-related dysregulation, or post-cardiac arrest reperfusion (38, 50–55). In patients with a normal ICP and CPP, TCD waveforms show a characteristic low resistance waveform that shows progressive changes with an increase in ICPs manifesting initially as resistive waveforms with decreased diastolic flow. Further increase in ICPs causes oscillating flow with reversal of diastolic flow before progressing to systolic spikes and then cessation of flow or cerebral circulatory arrest (Fig. 4). In the presence of an acoustic window, TCD can accurately predict impending cerebral herniation and can be a useful ancillary test for brain death evaluation (56). The World Brain Death Project currently recommends use of TCD as an alternate to conventional four-vessel cerebral angiography for brain death testing in adults when an ancillary test is indicated (57, 58). In addition, TCD waveforms can help to distinguish hyperemic intracranial hypertension, where increased blood flow drives increased ICP in a dysregulated brain, from oligemic intracranial hypertension, where CBF is reduced due to structural disease such as cerebral edema (Fig. 4; and **Supplementary Fig. 5**, http://links.lww.com/CCM/H285) (38, 59). This distinction can guide therapeutic interventions that may need a decrease in systemic blood pressure to target lower CPP in hyperemic intracranial hypertension compared with oligemic hypertension that may need augmentation of CPP and cerebral edema or CSF drainage targeted therapies. This may have potential value in the postoperative care for patients at risk for acute cerebral vascular dysregulation after carotid endarterectomy, carotid stenting, or coronary artery bypass. ICP can be estimated using TCD derived peak, diastolic, and mean flow velocity. Pulsatility Index or PI (Peak flow velocity–End-Diastolic Velocity/Mean Flow Velocity) represents distal cerebrovascular resistance and can be used in global ABI as an ICP surrogate (60). The invasive versus non-invasive Measurement of intracranial PRESSure in brain Injury Trial (IMPRESSIT-2) trial investigated noninvasive ICP derived from TCDs and showed high negative predictive value of TCDs-derived ICP in ruling out intracranial hypertension (3). Wide-scale application of TCD is limited by the lack of acoustic windows in 15–30% of patients and the high level of expertise required in interpretation but is slowly gaining popularity with increased use of point-of-care ultrasound in critical care (59, 61).

Other devices have been investigated to measure noninvasive ICP using waveform analysis derived from pulsatility of intracranial circulation using a scalp sensor (Brain4care, Sao Paolo, Brazil) or changes in ear pressure using a tympanic sensor (62, 63). These devices need high quality evidence before wide-scale application.

Cerebral Oxygenation

Brain tissue oxygenation appears to be a suitable target for neuromonitoring given that oxygen delivery is impacted by CBF and cerebral metabolism and is responsive to systemic derangements in critically ill patients. By evaluation and management of reduced tissue oxygen delivery, cerebral oxygenation monitoring can potentially mitigate SBI due to hypoxia or ischemia.

"Near-infrared spectroscopy (NIRS)" offers a noninvasive bedside measurement of direct regional cerebral arteriovenous (mixed) brain oxygenation using wavelength-dependent light attenuation to measure hemoglobin concentration (Fig. 2) (35, 64–67). It is most useful in serial monitoring for scenarios where patients can serve as their own controls since it calculates changes from baseline, rather than absolute oxygenation values (67). This has found use in intraoperative neuromonitoring for cardiothoracic procedures at high risk of neurologic deterioration (68). Clinical application of the device is limited in patients with scalp hematomas due to interference from ambient light and dark skin tone (69).

An invasive $Pbto_2$ monitor is typically placed in the nondominant frontal lobe in diffuse ABI to monitor the perilesional area at risk for SBI in focal lesions. A reliable consistent signal may take several hours to stabilize, and oxygen thresholds depend on probe position, mandating a post-procedural CT after probe placement (5). The target for $Pbto_2$ is greater than 15–20 mm Hg in parenchyma and drift causes a lack of accuracy after 7–10 days of insertion. $Pbto_2$ monitoring can detect reduced oxygen delivery even when ICP and CPP are within normal thresholds and allows tailoring of targets such as ventilator targets (Fio_2, positive end-expiratory pressure, CPP, $Paco_2$), hemoglobin concentration, and ICP to meet metabolic demands

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of the individual brain (70, 71). Decreasing $Pbto_2$ and CBF with normal ICP in a sedated afebrile patient may reflect reduced delivery, warranting an increase in MAP and CPP or assessing for anemia. $Pbto_2$ has been investigated as a marker for early detection of delayed cerebral ischemia (DCI) in aSAH given demonstrated brain hypoxia in SAH patients with normal ICPs (72). When used with ICP monitoring, $Pbto_2$ can guide titration of tiered medical and surgical ICP/CPP therapies such as analgesia, sedation, hyperosmolar therapy, ventriculostomy, neuromuscular blockade, therapeutic hypothermia, and craniectomy as recommended by the Seattle International Severe TBI Consensus Conference (**Supplementary Fig. 6**, http://links.lww.com/CCM/H285) (5, 73). Due to the demonstrated association between reduced $Pbto_2$ and poor neurologic outcomes, optimization of $Pbto_2$ has been explored as a target of therapy to improve survival in severe traumatic brain injury trials after successful phase II studies Brain Oxygen Optimization in Severe TBI, Phase 3 [BOOST-3], Impact of Early Optimization of Brain Oxygenation on Neurological Outcome After Severe Traumatic Brain Injury [OXY-TC], and Brain Oxygen Neuromonitoring in Australia and New Zealand Assessment [BONANZA] (5, 70–72, 74–79).

"Jugular venous oxygen saturation ($Sjvo_2$)" measures the percentage of oxygenated hemoglobin in cerebral outflow, which provides an indirect evaluation of brain tissue oxygenation and metabolism. $Sjvo_2$ is measured through a fiberoptic catheter positioned in the jugular venous bulb accessed intravenously through the internal jugular vein and has a normal range of 55–75%. Low $Sjvo_2$ reflects an increase in brain oxygen extraction due to reduced delivery such as vasospasm or ischemia, which can be confirmed by concurrent measurement of CBF or $Pbto_2$. Low $Sjvo_2$ can also be caused by increased cerebral metabolic demand from fever, shivering, agitation, or cortical spreading depolarization, in which case CBF and $Pbto_2$ can be normal or high. This helps in targeting therapy. Treatment should target an increase in perfusion and/or oxygenation in the former, while management should be focused on identifying and aggressively treating the cause of increased cerebral metabolic demand in the latter case. $Sjvo_2$ may be elevated in high delivery states such as hyperemia, hyperoxia, arteriovenous shunting or in extensively infarcted brain, in which case, treatment should be targeted toward lowering CBF and CPP. $Sjvo_2$ monitors are sensitive to global changes in cerebral oxygen delivery or metabolism but often require additional ICP/CPP/$Pbto_2$ monitoring data obtained invasively to provide guidance for specific interventions. The monitors require frequent recalibrations and have a risk of line-associated infection and venous thrombosis similar to central venous lines. In addition, maintaining the blood pressure at a higher-than-normal level in a patient with severe head injury using $Sjvo_2$ targeted therapy might result in an increased frequency of adult respiratory distress syndrome and acute renal failure from the additional fluid or pressor agents (80). Due to these limitations and the lack of robust evidence showing improved outcomes, $Sjvo_2$ monitoring is not frequently used despite remaining in the severe TBI management guidelines (81).

Cerebral Autoregulation

CA is the inherent ability of the brain to maintain perfusion over a wide range of physiologic variations in systemic blood pressure or carbon dioxide. Impaired CA in ABI renders the injured brain unable to maintain perfusion over systemic fluctuations, leading to compounded SBI from ischemic and hyperemia. Static CA can be assessed using TCD or NIRS to monitor changes in CBFV in response to physiologic maneuvers such as hyperventilation or induced hypertension (Supplementary Fig. 3, http://links.lww.com/CCM/H285) (73). Dynamic CA can be assessed using continuous monitoring of cerebral blood flow velocity (CBFV) or ICPs, time-synchronized with systemic MAP. This is measured as a moving Pearson correlation coefficient between MAP and ICP (pressure reactivity index [PRx]), between cerebral perfusion pressure and CBFV (mean flow index [Mx]) (28, 82) or between arterial blood pressure and CBFV (Mxa). A linear relationship between ICP/CBFV and MAP denotes a lack of CA (**Supplementary Fig. 8**, http://links.lww.com/CCM/H285). A high PRx cutoff of greater than 0.3 denotes poor autoregulation, while a low PRx less than 0.05 suggests preserved CA. Although PRx use is more widespread due to greater availability of ICP monitoring compared with TCD expertise, both PRx and Mx have shown a strong association with clinical outcome in critically ill patients with both traumatic and nontraumatic brain injury (83, 84). In patients with TBI, Brain Trauma Foundation guidelines and the Seattle consensus conference recommend

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autoregulation-guided CPP thresholds, with lower CPP targets in patients who demonstrate absence of autoregulation and higher CPP targets in patients with intact CA (51, 73).

Dynamic CA can be highly dependent on the physiologic state of each patient and varies with fluctuations in ICP, compliance, systemic blood pressure, minute ventilation, and body temperature. Bedside continuous monitoring of a patient's individual PRx or Mxa over these physiologic fluctuations typically manifests as a U-shaped curve, and the bottom of the curve can help identify the patient's optimal target CPP (CPPopt), where the patient's CA is physiologically most optimum (84, 85). If a patient's U-shaped curve is shifted to the left, a predetermined threshold CPP of 70 mm Hg though within the "normal range," may result in high PRx, predisposing the patient to hyperemia. CPPopt is typically calculated over 4 hours of data and is itself a dynamic metric that requires a MMM framework to support big data analysis for bedside visualization. This limits wide-scale applicability at this time. The Targeting Autoregulation-Guided Cerebral Perfusion Pressure after Traumatic Brain Injury (COGiTATE) trial recently investigated the feasibility of such autoregulation and optimal CPP-guided clinical algorithms and shows a promising approach for future outcome-oriented trials (86, 87).

ELECTRICITY

Electrophysiology

"Continuous Electroencephalography (cEEG)" has raised awareness of the prevalence of nonconvulsive seizures in critical illness irrespective of neurologic diagnosis (**Supplementary Fig. 7**, http://links.lww.com/CCM/H285) (88, 89). cEEG is recommended for seizure detection in all patients with impaired consciousness after ABI, in patients who have had a cardiac arrest, and in all patients who have had clinical seizures and have not returned to baseline (5). cEEG-derived markers can also be a useful tool for early detection of ischemia in patients with unreliable or poor neurologic examination (90–92). Conversely, cEEG can characterize distinct levels of consciousness and identify hidden consciousness in unresponsive patients (93, 94). Electrophysiology information from cEEG is a key part of the multimodal approach to neuroprognostication in many types of ABI, including in comatose survivors of cardiac arrest (95, 96). Surface EEG is prone to artifacts, interference from ICU equipment, skin breakdown, and requires technical support for electrode placement. Intracortical EEG, while invasive, may be potentially superior to scalp EEG but has not been explored beyond TBI and SAH (97). Point-of-care EEG systems, specifically utilizing automated computational algorithms for quantitative EEG analysis have facilitated bedside visualization for targeting timely clinical interventions by ICU staff, replacing the need for raw EEG interpretation (Persyst, Solana Beach, CA) (98–101).

"The bispectral index (BIS) monitor," another electrophysiology device often used intraoperatively, uses processed electrographic signals through a proprietary algorithm to generate a value (BIS) reflecting the patient's level of consciousness in response to sedation. A BIS value ranges from 0 to 100, with 40 to 60 representing deep sedation consistent with general anesthesia. Critical care applications of BIS were explored for ensuring adequate sedation in paralyzed patients receiving neuromuscular blocking drugs or as a surrogate for depth of anesthesia to titrate sedation during tiered management of intracranial hypertension (102, 103). Concerns about BIS's reliance on muscle activity regardless of level of awareness; a source of electroencephalographic input limited to bi-frontal leads; anesthesia awareness despite target ranges in several studies; and low-quality evidence guiding its use have limited its routine use as a standard in the ICU. A component of the BIS algorithm called suppression ratio (SR) quantifies the proportion of burst suppression EEG pattern or isoelectric activity but is confounded by the same limitations as BIS.

"Somatosensory evoked potentials (SSEPs)" are CNS responses elicited by stimulation of peripheral nerves, typically the median, ulnar, or posterior tibial nerves, to detect a focal lesion in the dorsal column-lemniscal pathway via the spinal cord, brain stem, and thalamus. Impaired or absent SSEP waveforms can be caused by a pathology in the peripheral nervous system, posterior columns of the spinal cord, brain stem or cortex along the path between the electrical stimulus and cortical response. Absence of cortical (N20) waveforms bilaterally is the most widely researched SSEP and is a reliable poor prognostic indicator after cardiac arrest and traumatic coma with a variable sensitivity but a high specificity of greater

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than 90% (104). However, the need for specialized equipment, variable accuracy in severe core hypothermia, interference from background artifacts, and current literature on prognostication confounded by early withdrawal of life-sustaining therapies has limited its widespread use (8, 105, 106).

CEREBRAL BIOCHEMISTRY

"Cerebral microdialysis catheters" are invasive monitors that enable sampling of the brain interstitial substrates such as cerebral glucose, lactic acid, pyruvate, glutamate, and glycerol in patients with ABI. A high lactate/pyruvate ratio or more than 25, and especially more than 40, is a biomarker of reduced substrate delivery (oxygen or glucose), or impaired oxidative metabolism due to mitochondrial dysfunction, which can be distinguished by concurrent monitoring of reduced or normal $Pbto_2$ levels, respectively (107, 108). CMD data combined with ICP and $Pbto_2$ can thus serve as a target for interventions (109). Cellular level changes detected by CMD can detect ischemia, hypoxia, or mitochondrial dysfunction before conventional neuromonitoring techniques or clinical deterioration. CMD metrics can predict DCI in aneurysmal SAH 11–23 hours before change in clinical examination, and CMD-based interventions have been associated with a low incidence of DCI (110, 111). The need for frequent sampling and specialized infrastructure makes CMD a resource-intensive modality. In addition, there is a wide variability in CMD variables with a lack of validated thresholds for different clinical types of ABI. Further research is needed to assess whether CMD-based targets can help tailor interventions and improve outcomes in patients at risk of SBI (5).

"Serum and CSF biomarkers" such as neuron-specific enolase (NSE), 14-3-3 protein, and tau protein can be useful markers to stratify the degree of neuronal injury (10). When taken into consideration in combination with other prognostic markers, high serum NSE values within 48–72 hours of cardiac arrest or high serum neurofilament light chain values 24 hours after cardiac arrest predict a poor prognosis for neurologic recovery in comatose cardiac arrest survivors (112–114). Routine use of such biomarkers is limited due to prolonged turn-around times of 2–5 days in most hospitals for the commercially available assay for NSE. The use of S100 calcium-binding protein, Tau, and glial fibrillary acidic protein in neuroprognostication in ABI is still unclear until more data shows new information.

MULTIMODALITY MONITORING

Continuous monitoring allows us to investigate the interplay of neurologic and systemic physiologic phenomena in critically ill patients. A time-synchronized integration of neurologic examination with other physiologic parameters via invasive and noninvasive modalities is called MMM (Supplementary Figs. 4, 6, and 8, http://links.lww.com/CCM/H285). Clinical algorithms focused on a single target, whether it be ICP or CPP, are neither physiologically intuitive nor have they shown benefit in outcomes-based research (**Table 1**) (37). Standard CPP-guided approach in severe TBI showed more pulmonary complications than ICP-guided approach, but there was no difference in the neurologic outcome (80). Despite failure to reach primary endpoints of improving neurologic outcomes, such investigations have emphasized the crucial role of monitoring brain and systemic physiology in patients at risk of SBI when evaluating neurologically targeted interventions. MMM has also highlighted the dynamic physiology of SBI and uncovered the dependency of physiologic thresholds on the degree of CA and intracranial compliance. Neuroprognostication guidelines have consistently emphasized a multimodal approach including physiologic, clinical, and radiographic markers in ABI (8, 121, 122). MMM data from clinical trials like COGiTATE and BOOST has opened doors for a framework for research into individualized targets for therapy. Increased access to bedside MMM platforms (ICM+, University of Cambridge, Cambridge, United Kingdom; Moberg CNS Monitor, Ambler, PA) hopefully will allow rigorous investigations studying the impact of patient-centric autoregulation-based algorithms incorporating metrics like PRx, Mxa, or CPPopt guided interventions on clinical outcomes (28, 86, 123).

CONCLUSIONS

SBI is multifaceted, dynamic, and complex. MMM has opened doors for new understanding of ABI mechanisms that can guide individualized targets for interventions in critically ill patients susceptible to brain injury. Technological advances facilitating wider

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TABLE 1.
Tabulated Thresholds of Various Multimodality Monitoring Devices Used in Neurologic Monitoring With the Pro and Cons Related to the Modality

Monitoring Device	Pros and Cons	Treatment Thresholds
Structure		
Automated pupilometer	Pro: Consistent reliable pupil measurements with quantitative pupillometry Con: Costly compared with flashlight Variability of measurements with ambient light, orbital pathology, agitation, or medications	Thresholds for abnormal cutoffs associated with an increase in ICP: Pupillary asymmetry> 0.5 mm Pupil constriction velocity < 0.8 mm/s Decrease in pupil diameter < 10% Latency has not found clinical use Difference in NPi between right and left pupils of ≥ 0.7 (16) NPi > 3
CT-/MRI-based metrics	Pro: Provides structural evaluation of ABI Portable bedside CT and MRI scanners available Con: Shows downstream effects of ABI likely irreversible CT may not show mid ABI Serial assessments limited by lack widespread availability of portable scanner and radiation risk	Marshall classification for TBI Alberta Stroke Program Early CT Score for ischemic stroke Modified Fisher grade for subarachnoid hemorrhage Graeb score for intraventricular hemorrhage Used to estimate severity of injury but use as a serial target for therapy is limited (115) Extensive areas of reduced apparent diffusion coefficient on brain MRI at 2 to 7 d after cardiac arrest have been used a biomarker for poor prognostication in comatose patients after cardiac arrest (8)
TCD parameters	Pro: dynamic bedside non invasive assessment Provides ability to measure CBF continuously in response to systemic changes Con: Lack of widespread availability of TCD expertise. 15–35% patients may not have acoustic windows High sensitivity but low specificity for detecting vasospasm specially in moderate elevation of velocities	Mean flow velocity for middle cerebral artery 50–80 cm/s Pulsatility index 0.6–1.2 (21, 60) MCA MFV > 200 cm/s, daily increase in velocity by 50 cm/s or Lindegaard ratio (ratio of intracranial MCA velocity to extracranial internal carotid artery velocity) > 6 high positive predictive value in predicting clinically significant vasospasm MCA MFV < 80 cm/s high negative predictive value in predicting clinically significant vasospasm (21, 24, 25) Persistence of oscillating flow or systolic spikes < 50 cm/s, < 200 ms duration predict cerebral circulatory arrest (56)
Plumbing/pressure		
Intraparenchymal CBF monitors	Pro: Direct continuous measurement of regional CBF Con: Invasive. Risk of hemorrhage, infection, dislodgment on movement Accuracy affected by location of the probe in proximity to large vessels and brain pyrexia. Cannot be used in patients on systemic anticoagulation	Normal range adults 20–50 mL/100 g/min for predominantly white matter location with higher values close to gray matter (35)

(*Continued*)

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TABLE 1. (*Continued*).

Tabulated Thresholds of Various Multimodality Monitoring Devices Used in Neurologic Monitoring With the Pro and Cons Related to the Modality

Monitoring Device	Pros and Cons	Treatment Thresholds
ICP/CPP (strain gauge, fiberoptic, or EVD)	Pro: Direct continuous measurement of ICP EVD allows cerebrospinal fluid drainage Con: Invasive. Risk of hemorrhage, infection, dislodgment on movement. Intraparenchymal monitor drifts in 5–7 d rendering it inaccurate. Cannot be used in patients on systemic anticoagulation	ICP thresholds for treatment > 20–25 mm Hg CPP thresholds < 60 or > 80 mm Hg
ONSD	Pro: Noninvasive. Allows serial assessments. Does not need patient cooperation Con: Variable optic nerve anatomy. Wide ONSD seen in normal healthy individuals and normal ONSD seen in intracranial hypertension with sudden increase in ICP	Diameters of > 5 to 5.9 mm (variable based on study) correlates with high ICP
Near-infrared spectroscopy	Pro: Noninvasive. Allows serial assessments Con: Affected by vasopressors. Accuracy affected in scalp hematomas due to interference from ambient light, and dark skin color	Regional mixed oxygen saturation > 60% (65)
$Pbto_2$	Pro: Measures substrate delivery directly Con: Invasive. Risk of hemorrhage, infection, dislodgment on movement. Cannot be used in patients in systemic anticoagulation. Accuracy can be affected by location in gray vs white matter, in ischemic vs dead brain	$Pbto_2$ < 15–20 mm Hg have been associated with ischemia (67)
$Sjvo_2$	Pro: Global measure of oxygen consumption and/or delivery Con: Invasive. Risk of hemorrhage, infection, dislodgment on movement. Cannot be used in patients in systemic anticoagulation. Risk of venous thrombosis in internal jugular	$Sjvo_2$ < 55 and > 75% are abnormal (70)
CA	Pro: Suitable target for guiding therapies Con: Dynamic metric that may fluctuate within the same patient over hours. Dynamic CA testing for optimal CPP based on CA requires monitoring framework that is expensive and requires data science expertise	Mean flow index > 0.3 indicates disturbed autoregulation and lower than 0.05 good autoregulation (81) PRx > 0.3 critical threshold for determining fatal outcome in severe TBI (81) PRx > 0.2 associated with poor outcome after cardiac arrest (83)
Electricity		
Electroencephalography	Pro: Noninvasive. Sensitive to ischemic and hypoxic changes in brain in addition to diagnosing seizures Con: Qualitative review requires expertise. Quantitative EEG requires special equipment and software that is expensive	Delta/alpha power ratio > 3.7 ~ radiologically confirmed acute infarct (116) Alpha Delta Ratio > 10% change post-stimulation predictive of delayed cerebral ischemia Absence of reactivity, reduced alpha variability, decrease in alpha-delta ratios, and absence of sleep architecture have been associated with worse outcomes (89–91) Seizures based on Salzburg criteria (117)

(*Continued*)

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TABLE 1. (*Continued*).

Tabulated Thresholds of Various Multimodality Monitoring Devices Used in Neurologic Monitoring With the Pro and Cons Related to the Modality

Monitoring Device	Pros and Cons	Treatment Thresholds
Bispectral index	Pro: Noninvasive. Inexpensive monitor Con: Limited EEG from bifrontal leads as input hence inaccurate for global cerebral assessment. Awareness during anesthesia known despite bispectral index values in thresholds for deep sedation	90 to 100 indicates a state of wakefulness (118) Zero indicates absence of brain electrical activity 40–60 targeted for general anesthesia 60–80 targeted for light to moderate sedation
Air/composition		
Cerebral microdialysis	Pro: Measures cellular level changes Con: Hourly bedside sampling with dedicated infrastructure needed. Has to be used in conjunction with other multimodality monitoring. Measures after effects of ABI	Lactate pyruvate ratio > 25 and > 40 both reported as thresholds for cerebral metabolic distress (107, 119) Abnormal glucose below 1 mmol/L (± 0.15 mmol/L) Abnormal glutamate > 20 µmol/L Abnormal glycerol > 50 µmol/L
Serum biomarkers	Pro: Serum-based tests hence convenient to use in ICU Con: Limited availability to process samples hence increased turn-around time. Sensitive but not specific to cause of ABI. Predictive value depends on time of sample relative to ABI	Neuron-specific enolase levels for prediction of poor outcome with specificity > 95%, upper limits of the prediction interval: 70.4 ng/mL at 24–48 hr and 58.6 ng/mL at 48–72 hr (120)

ABI = acute brain injury, CA = cerebral autoregulation, CBF = cerebral blood flow, CPP = cerebral perfusion pressure, EEG = electroencephalography, EVD = external ventricular drainage, ICP = intracranial pressure, MCA = middle cerebral territory, MFV = mean flow velocity, NPi = neurologic pupillary index, ONSD = optic nerve sheath diameter, $Pbto_2$ = brain tissue oxygen tension, PRx = pressure reactivity index, $Sjvo_2$ = jugular venous oxygen saturation, TBI = traumatic brain injury, TCD = transcranial Doppler.

accessibility of advanced neuromonitoring capabilities will make it possible to conduct rigorous research trials that could inform outcome-changing paradigms.

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